

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

- 1 (Original) A method of magnetic resonance imaging (MRI) for in vivo mapping of concentration of a target metal ion in at least one tissue, comprising the steps of:  
administering an MRI contrast agent, said contrast agent selectively sensitive to amount of said target metal ion, said contrast agent comprising:  
a complexing agent comprising a non-hydrogen imaging nucleus, said complexing agent binding to said target metal ion;  
acquiring imaging signals via at least one imaging scan of said imaging nucleus;  
generating at least one image map comprising intensity of an image pixel derived from said imaging signal acquired during said imaging scan(s); and  
correlating intensity of said image pixel at any point on said image map or on a subtractive composite of said image maps with concentration of said target metal ion in the tissue(s) at said mapping point.
- 2 (Original) The method of claim 1, wherein selectivity of the contrast agent for said target metal ion is about 100-fold greater than selectivity of the contrast agent for other metal ions in vivo.
- 3 (Original) The method of claim 1, wherein the target metal ion is  $\text{Zn}^{+2}$  or  $\text{Cu}^{+2}$ .
- 4 (Original) The method of claim 1, wherein the imaging nucleus is  $^{19}\text{F}$ .
- 5 (Original) The method of claim 1, wherein said imaging nucleus is introduced into said complexing agent via derivatization of said complexing agent such that one or more hydrogen atoms comprising said complexing agent are replaced by said imaging nucleus or by a functional group comprising one or more of said imaging nuclei.
- 6 (Original) The method of claim 5, wherein the complexing agent is a fluorinated derivative of 1,2-bis-(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid, ethylene glycol bis( $\beta$ -aminoethyl ether)-N,N,N',N'-tetraacetic acid or ethylenediaminetetracetic acid.

7 (Original) The method of claim 1, wherein the complexing agent is an apo-metallothionein covalently linked with a fluorine-containing compound.

8 (Original) The method of claim 7, wherein the fluorine-containing compound is Oregon Green.

9 (Original) The method of claim 1, said complexing agent further comprising one or more functional groups, said functional groups enhancing in vivo biological acceptability of the contrast agent.

10 (Original) The method of claim 9, wherein the functional group(s) comprises a targeting vector specific for a receptor.

11 (Currently Amended) The method of claim ~~8~~ 9, wherein the functional group(s) enhances penetration of the contrasting agent across a biological barrier.

12 (Currently Amended) The method of claim ~~10~~ 11, wherein the biological barrier is the blood-brain barrier.

13 (Original) The method of claim 1, wherein the contrast agent is administered orally, intravenously, transdermally, or via inhalation or direct administration to the tissue(s) or to an organ comprising the tissue.

14 (Original) The method of claim 1, wherein binding said target metal ion by the contrast agent measurably alters a nuclear longitudinal relaxation time of said imaging nucleus, a nuclear transverse relaxation time of said imaging nucleus or a combination thereof, wherein intensity of said image signal from said imaging nucleus is sensitive to said relaxation time(s).

15 (Original) The method of claim 14, wherein alteration of said longitudinal and/or transverse relaxation times independently comprises a lengthening and/or a shortening of said relaxation times of about 1.5-fold to about 15-fold of the relaxation time(s) of the contrast agent prior to binding said target metal ion.

16 (Original) The method of claim 15, wherein said longitudinal and said transverse relaxation times are shortened about 2-fold to about 7-fold.

17 (Original) The method of claim 14, wherein the contrast agent is 1,2-bis-(2-amino-5-fluorophenoxy)ethane-N,N,N',N'-tetraacetic acid or 1,2-bis-(2-amino-5-trifluoromethylphenoxy)ethane-N,N,N',N'-tetra acetic acid, said target metal ion is  $\text{Zn}^{+2}$  and said transverse relaxation time is measurably shortened.

18 (Original) The method of claim 17, wherein a first MRI image map utilizing a long relaxation delay for transverse relaxation ( $T_2$ ) and a second MRI image map utilizing a short relaxation delay for transverse relaxation are generated from imaging scans such that said first MRI image map is subtracted from said second MRI image map thereby obtaining a high intensity image signal map of said  $\text{Zn}^{+2}$  concentrations.

19 (Original) The method of claim 18, wherein the imaging scan utilizes a spin-echo sequence.

20 (Original) The method of claim 1, further comprising the step of: diagnosing a disease state wherein the concentration of said target metal ion in the tissue(s) is characteristic of the presence or absence of the disease state.

21 (Original) The method of claim 20, wherein the disease state is Alzheimer's disease and the target metal ion is  $\text{Zn}^{+2}$  or  $\text{Cu}^{+2}$ .

22 (Original) The method of claim 20, wherein the disease state is prostate cancer and the target metal ion is  $\text{Zn}^{+2}$ .

23 (Original) The method of claim 20, further comprising the step of: monitoring the efficacy of a therapeutic regimen to treat said disease state wherein the concentration of said target metal ion in the tissue(s) is characteristic of progression or regression of the disease state.

24 (Original) A method of magnetic resonance imaging (MRI) for in vivo mapping of concentration of  $\text{Zn}^{+2}$  ion in at least one tissue, comprising the steps of: administering 1,2-bis-(2-amino-5-fluorophenoxy)ethane-N,N,N',N'-tetraacetic acid or 1,2-bis-(2-amino-5-trifluoromethylphenoxy)ethane-N,N,N',N'-tetra acetic acid as a contrast agent, wherein the fluorine imaging nucleus comprising the contrast agent is selectively sensitive to the amount of the  $\text{Zn}^{+2}$  ion, acquiring imaging signals via at least one imaging scan of said imaging nucleus; generating at least one image map comprising intensity of an image pixel derived from said image signal acquired during said imaging scan(s); and correlating intensity of said image pixel

at any point on said image map or on a subtractive composite of said image maps with concentration of the  $\text{Zn}^{+2}$  ion in the tissue(s) at said mapping point.

25 (Original) The method of claim 24, said contrast agent further comprising one or more functional groups, said functional groups enhancing in vivo biological acceptability of the contrast agent.

26 (Original) The method of claim 25, wherein the functional group(s) comprises a targeting vector specific for a receptor.

27 (Original) The method of claim 25, wherein the functional group(s) enhances penetration of the contrasting agent across a biological barrier.

28 (Original) The method of claim 27, wherein the biological barrier is the blood-brain barrier.

29 (Original) The method of claim 24, wherein the contrast agent is administered orally, intravenously, transdermally, or via inhalation or direct administration to the tissue(s), or to an organ comprising the tissue.

30 (Original) The method of claim 1, wherein binding the  $\text{Zn}^{+2}$  ion by the contrast agent measurably shortens a nuclear transverse relaxation time of said fluorine imaging nucleus, wherein intensity of said image signal from said imaging nucleus is sensitive to said transverse relaxation time.

31 (Original) The method of claim 30, wherein said transverse relaxation time is shortened about 1.5-fold to about 15-fold of the transverse relaxation time of the contrast agent prior to binding the  $\text{Zn}^{+2}$  ion.

32 (Original) The method of claim 30, wherein said transverse relaxation time is shortened about 2-fold to about 7-fold.

33 (Original) The method of claim 24, wherein the imaging scan utilizes a spin-echo sequence.

34 (Original) The method of claim 24, further comprising the step of: diagnosing a disease state wherein the concentration of said target metal ion in the tissue(s) is characteristic of the presence or absence of the disease state.

35 (Original) The method of claim 34, wherein the disease state is Alzheimer's disease or prostate cancer.

36 (Original) The method of claim 34, further comprising the step of: monitoring the efficacy of a therapeutic regimen to treat said disease state wherein the concentration of the  $\text{Zn}^{+2}$  ion in the tissue(s) is characteristic of progression or regression of the disease state.